REMARKS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

It is requested that prosecution of this application be continued under Rule 129(a). The required fee is submitted herewith.

Claims 33, 37 and 41 have been revised to define the invention with additional clarity. Claims 34-36 and 38-40 have been cancelled and new claims 45-48 have been added. The claims as presented are fully supported by an enabling disclosure.

Claims 33 and 37 have been revised so as to use language more consistent with that used in the allowed parent case. The Examiner will note that the fact that the present claims are drawn to a treatment of "a disorder mediated by an immune reaction to an antigen possessed by said human", indicates that the condition being treated is pre-existing, that is, the antigen (an auto-antigen or otherwise) is present and the condition is on-going when antibody treatment commences. Such treatment is

distinct from reports in the art of essentially simultaneous exposure to antigen and antibody.

Claim 41 has also been amended to correspond more closely to the language of the claims of the allowed parent case.

Claims 33-44 stand provisionally rejected as representing obviousness type double patenting over claims 34 and 36-45 of Application No. 08/289,532. The Examiner is again urged to hold this rejection in abeyance until this case is otherwise in condition for allowance.

Claims 33-44 stand rejected under 35 USC 103 as allegedly being obvious over Qin et al in view of Waldmann (Ann. Rev. Immunol.), Waldmann (Am. J. Kid. Dis.) and Carteron et al. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

Qin et al relates to the induction of hemopoietic chimerism by the use of bone marrow transplantation (BMT). Establishment

of the BMT means that the immune system of the recipient recognizes as "self" not only his/her own antigens, but antigens from the donor of the bone marrow. Accordingly, the recipient becomes "chimeric" at least as far as antigens recognized as "self" are concerned in the sense that the recipient now recognizes antigens from two different people as "self". Once this state has been achieved, the recipient does not reject skin grafts from the bone marrow donor. The Qin et al paper addresses the problem of getting the BMT established and describes the use of various combinations of antibodies to achieve this, including the use of at least one non-depleting anti-CD4 antibody.

There is no doubt but that the non-depleting anti-CD4 antibodies are <u>not</u> inducing long-term immunological unresponsiveness to the graft; on the contrary, this unresponsiveness is a direct result of the BMT. The Examiner appears to appreciate this since he does not refer specifically to the skin grafts, but rather contends that the claims of the present application cover the induction of long-term unresponsiveness to grafts, including BMT.

Applicants have previously pointed out that there is no reason to suppose that the antibodies of Qin et al are having anything other than a temporary immunosuppressive effect which merely allows the BMT to become established, whereupon the BMT has the effect of making the recipient of the BMT unresponsive to the BMT itself (since the antigens of the BMT are recognized as self). Those prior arguments are incorporated herein by reference. Should the Examiner be of a different view, he is urged to specify what teaching(s) of the reference (or otherwise) supports his position.

The secondary references upon which the Examiner relies are review articles which add nothing substantive to the disclosure of Qin et al. In Ann Rev Immunol, p. 427, Waldmann says:

> "Recently, we have shown (75) that tolerance can be induced in CD4 T cells without the need for their depletion. This was accomplished by high does of the rIgG2a Mab. If this form of "tolerance therapy" could be extended over stronger antigenic barriers then there would be obvious clinical application in transplantation and correction of autoimmunity."

Reference 75 is a paper said to be "submitted" and, although the above comments make no mention of bone marrow transplantation, the referenced paper is entitled "Induction of Classical Transplantation Tolerance in the Adult". Bone Marrow Transplantation to Secure Tolerance in the Adult", which strongly suggests the subsequently published Qin et al, J. Exp. Med. article cited by the Examiner and discussed above.

In Am J Kid Dis, p. 156, Waldmann says:

> ". . . where the test graft was bone marrow we have been able to produce long-term tolerance of CBA mice to B10.Br marrow.[5] In fact, the combination of CD4 and CD8 MoAbs together with a bone marrow graft is tolerogenic for a subsequent skin graft from he same donor. By this protocol one achieves long-term chimerism, long-term skin graft survival, and tolerance to subsequent skin grafts. The bone marrow graft somehow provides the last component of a synergistic tolerogenic inoculum."

Reference 5 is again said to be "submitted" and is identified as "Qin S, Cobbold S P, Waldmann H; Induction of Classical Transplantation Tolerance in the Adult" which again strongly suggests the Qin et al, J. Exp. Med. paper.

It is clear from the foregoing that Waldmann is not suggesting that the antibodies are inducing tolerance (long term unresponsiveness) to the skin grafts and that the BMT is an essential component before this can be achieved.

In addition to the above, the Examiner is reminded that the claims as now presented are drawn to the treatment of a condition which pre-existed at the time of the antibody treatment. This is in contrast to Qin et al wherein the BMT was administered with or after the antibody treatment.

The Examiner also relies upon Carteron et al. However, it is not clear to Applicants why one of ordinary skill would have combined the teachings of Qin et al (and Waldmann) with Carteron et al. Even if the combination had been made, the present invention would not have been reached.

Applicants have previously discussed the significance of references such as Carteron et al which relate to fragments of depleting anti-CD4 antibodies. Those comments are incorporated

herein by reference and the Examiner is again referred to the Crowe declaration of July 7, 1995.

Applicants assume from the Examiner's reliance on Carteron et al that he is suggesting that one of ordinary skill would have assumed that depletion was irrelevant to tolerance induction. As indicated by Dr. Crowe in his declaration, this is not correct. The fact that fragments of depleting anti-CD4 antibodies were able to induce tolerance to an antigen by some unknown mechanism (albeit one which presumably did not involve depletion) did not make it obvious that non-depleting anti-CD4 antibodies would act in the same way. Given that the effect of whole non-depleting antibodies could not have been predicted based on what was known about the properties of depleting anti-CD4 antibodies and their fragments, it follows that it also could not have been predicted that fragments of non-depleting anti-CD4 antibodies would be capable of inducing tolerance.

As to the Examiner's apparent suggestion that, in view of this argument, Applicants may not have enabled the use of

fragments of non-depleting antibodies in tolerance induction, the Examiner is reminded that Applicants, not the art, established that whole non-depleting anti-CD4 antibodies are capable of inducing tolerance. Since the whole antibody is non-depleting, the tolerance induction process is likely to involve either blocking or down-modulation (removal from the surface) of CD4 on CD4+ T-cells. Accordingly, the portion of the antibody which is lost in the process of preparing fragments would not likely affect the tolerance induction process.

Further support for this proposition can be found in a published paper by Bartholomew et al (copy attached). This relates to work on non-depleting anti-CD4 antibodies and shows that the whole antibody brings about dramatic down-modulation of CD4 on resting and activated CD4+ cells. While Fc region modulated cross-linking is essential to down-modulation on resting CD4+ T-cells, this was not essential for down-modulation of CD4 on activated CD4+ T-cells. Both $F(ab')_2$ fragments and Fc-defective antibody (produced by site directed mutagenesis) produced down-modulation of CD4 on activated T-cells and

tolerance induction does not require down-modulation on resting CD4+ T-cells.

The Examiner is urged to consider the foregoing comments. It is believed that having done so, he will find withdrawal of the rejection to be in order.

The Examiner is urged to consider the documents submitted herewith and initial and return the accompanying PTO 1449 Form.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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